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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,287	02/03/2005	Kenji Kogami	SAEG122.002APC	3585

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EXAMINER
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HAVLIN, ROBERT H

ART UNIT	PAPER NUMBER
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1626

NOTIFICATION DATE	DELIVERY MODE
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02/18/2009

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com  
eOAPilot@kmob.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/523,287	<b>Applicant(s)</b> KOGAMI ET AL.	
	<b>Examiner</b> ROBERT HAVLIN	<b>Art Unit</b> 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on 13 November 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 4-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2 and 4-8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 August 2007 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

**Status of the Claims:** Claims 1, 2, 4-8 are currently pending. Claim 1 and 7 were amended to add “in the presence of a carboxylic acid” to the reduction step. Claims 3 and 9 were cancelled.

### *Declarations*

1. The declaration of Takahashi Naoko under 37 CFR 1.132 filed 11/13/08 is insufficient to overcome the rejection of the claims based upon 35 USC 103 as set forth in the last Office action because: the declaration regarding the preparation and analysis of the physical properties of E and Z - N-monomethyl-3-oxo-3-(2-thienyl)propenamine is not persuasive as to the nonobviousness of the methyl modification on an amine group. First, the synthesis described in example 1 appears to be directly relevant to claims 4-6, while example 2 is merely the isomerization of example 1. This comparison does not provide an indication of how the synthesis method claimed uniquely favors Z over E, for example. The applicant bears the burden of demonstrating how the result is unexpected or unobvious from a synthetic chemistry perspective. From MPEP 716:

The evidence relied upon should establish “that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance.” Ex parte Gelles, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992) (Mere conclusions in appellants’ brief that the claimed polymer had an unexpectedly increased impact strength “are not entitled to the weight of conclusions accompanying the evidence, either in the specification or in a declaration.”); Ex parte C, 27 USPQ2d 1492 (Bd. Pat. App. & Inter. 1992) (Applicant alleged unexpected results with regard to the claimed soybean plant, however there was no basis for judging the practical significance of data with regard to maturity date, flowering date, flower color, or height of the plant.). See also In re Nolan, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977) and In re Eli Lilly, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) as discussed in MPEP § 716.02(c)..

Therefore, the declaration was not found persuasive as to the nonobviousness of the claims.

***Response to Applicant Arguments***

***Claim Rejections - 35 USC § 103***

2. Claims 1-2 were rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Chirality, 12:26-29 (2000) in IDS) in view of Makarova et al. (Russian Journal of General Chemistry, Vol. 71, No. 7, 2001, pp. 1126-1129.).

Applicant has amended the claims to introduce new limitations. Accordingly, new prior art is cited for the purposes of the amended claims: Gribble et al. (Org. Prep. Proc. Int. v. 17, p. 317-384 (1985)) and March (March's Advanced Organic Chemistry, 5th ed. (2001), Wiley, p. 2083).

Applicant argues:

1. Makarova does not teach the reduction of a beta-aminovinyl ketone in the presence of a carboxylic acid.
2. The examiner trivialized the structural differences of the method of Makarova relative to the obviousness rejection.
3. Liu provides a reasonable synthesis of N-methyl-3-hydroxy-3-(2-thienyl)propanamine employing a different method, thus one of ordinary skill in the art would not go beyond Liu to find an alternative.
4. Makarova's teaching renders the enzymatic transformation step unsatisfactory for its intended purpose, thus the combination does not lead to the claimed invention.

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In response:

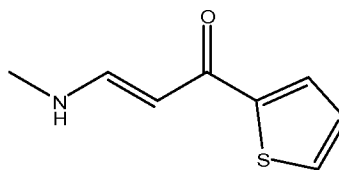
1. Reduction of compounds using methods as taught by Makarova is well known in the art. In addition, reductions using sodium borohydride is made chemoselective by using reagents such as carboxylic acids and is well known in the art and specifically taught by March in chapters 15 and 16, (see pages 1007-08, 1197-1203). In addition, Gribble teaches/reviews the well known use of carboxylic acids with the reducing agent of borohydride to tune the chemoselectivity of the reduction process.
2. The examiner has not trivialized the structural differences between the prior art and the claims, but recognizes that the level of ordinary skill in the synthetic arts is extremely high as evidenced by March. One of ordinary skill in the art would recognize the similarities between the prior art in combination with the knowledge of the predictability that the type of reaction performed on Makarova's compound would be expected to be applicable to the claimed method.
3. The motivation to find an optimal synthetic route to the drug precursor identified by Liu is very high due to the required stereoselectivity. Although Liu identifies an alternative synthetic route, one of ordinary skill in the synthetic chemistry art is motivated to search for an optimum route that has high yield combined with the desired stereoselectivity.
4. The enzymatic transformation step of Liu does not preclude the combination of the two prior art references because Liu teaches the

retrosynthetic strategy of deloxetine and identifies the desirable precursor of compound 6. The use of the enzyme highlights the importance of finding an alternative synthetic scheme which can stereoselectively produce the desired alcohol precursor of compound 6.

For the aforementioned reasons, **the rejection is amended to include a new prior art teaching the added limitation.**

Thus, Claims 1-2 are now rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Chirality, 12:26-29 (2000) in IDS) in view of Makarova et al. (Russian Journal of General Chemistry, Vol. 71, No. 7, 2001, pp. 1126-1129.), Gribble et al. (Org. Prep. Proc. Int. v. 17, p. 317-384 (1985)) and March (March's Advanced Organic Chemistry, 5<sup>th</sup> ed. (2001), Wiley, p. 2083).

3. Claims 4-5 were rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Chirality, 12:26-29 (2000) in IDS) in view of Makarova et al. (Russian Journal of General Chemistry, Vol. 71, No. 7, 2001, pp. 1126-1129.).



Claims 4 and 5 read on the following compound: 3-methylamino-1-(2-thienyl)-2-propen-1-one.

Applicant argues against the obviousness of claims 4 and 5; specifically that the prior art compounds are unrelated to the claimed synthetic pathway. One of ordinary skill in the art is capable of searching the prior art for compounds suggested by Liu et al. as desirable compounds and recognizing structural similarities (such as the methyl positional isomer). In addition, one of ordinary skill in the art would immediately

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recognize how to modify the reaction to produce the claimed invention based on the teachings of Makarova.

Applicant argues that the claimed compounds of claims 4 and 5 show unexpected properties because “it is impossible to directly or easily produce the variants of the [claimed compound],” and that the prior art is combined in a piecemeal fashion to arrive at the current invention. These arguments are unpersuasive because one of ordinary skill in the art of synthetic chemistry has a very high level of skill and can make inferences based on structural similarities, readily adapt chemical reactions to produce parallel transformations, and is capable of a large amount of experimentation to find the optimal reaction pathways with the best yield and/or purity. One of ordinary skill in the art has a strong motivation to look to alternate means of making the identified precursor and the application of well known techniques in the context where there is a substantial structural similarity would have been obvious. Therefore **this rejection is maintained.**

4. Claims 4 and 5 were rejected under 35 USC § 103(a) as being obvious over Cassella Farbwerke et al., Singh et al., and Bogdanowicz-Szwed et al..

Applicant argues that the compound is a useful intermediate and the prior art isomers do not readily lend themselves to structural similarity arguments. The examiner agrees because the prior art compounds are taught in a different context than the instant application. Therefore, **the rejection is withdrawn.**

5. Claim 6 was rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Chirality, 12:26-29 (2000) in IDS) in view of Makarova et al., Wright et al. (Journal of

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Medicinal Chemistry (1992), 35(22), 4061-8) and Guseinov et al. (CASREACT abstract # 122:132250 of Zhurnal Organicheskoi Khimii (1994), 30(4), 496-9).

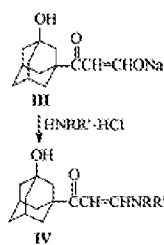
Applicant argues that the compounds and methods taught by Guseinov are not structurally related to the instant claims. Although applicant points to the differences of E/Z in the prior art vs. the claims, the method taught therein is relevant because of the amination technique. Furthermore, the Wright reference does teach the same stereochemistry as the claims. In addition, different substituents on the reactants do not negate the teaching of the method for structurally similar ligation elements of the reaction. Therefore, because the structural similarities are significant to the degree of the reactive elements, the argument is not persuasive and the rejection is maintained.


6. Claims 7 and 8 were rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Chirality, 12:26-29 (2000) in IDS) in view of Makarova et al., Wright et al. (Journal of Medicinal Chemistry (1992), 35(22), 4061-8) and Guseinov et al. (CASREACT abstract # 122:132250 of Zhurnal Organicheskoi Khimii (1994), 30(4), 496-9).

Applicant amended claim 7 by adding a new limitation of reduction in the presence of a carboxylic acid. To address this new limitation, the examiner cites new prior art reference of: Gribble et al. (Org. Prep. Proc. Int. v. 17, p. 317-384 (1985)), March (March's Advanced Organic Chemistry, 5th ed. (2001), Wiley, p. 2083), and Makarova-2 (Russian Journal of General Chemistry, Vol. 37, No. 8, 2001, pp. 1099-1101.).



Applicant argues that every claim element is not taught by the prior art. As discussed above in the prior office action, one of ordinary skill in the art has well within their technical grasp the ability to reformulate reactions using numerous methods available as taught by March and Liu, for example. In this case, one of ordinary skill is taught by Liu the desirability of developing an optimum synthetic route to the drug precursor. Using this motivation, one of ordinary skill in the art would know to look to the prior art and within their own abilities, and discover methods which are applicable to synthesize the precursor product such as is taught by Makarova-2. Makarova-2



teaches the structurally similar reaction of . While the adamantyl group is different, the reaction concept is exactly the same as is claimed and would predictably be applicable to a synthetic intermediate of the Liu precursor. The remainder of the claimed method is identical to that of claim 1 and is obvious in conjunction with the obvious method above. Therefore, **this rejection is maintained** and is amended as follows.

Claims 7 and 8 are now rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Chirality, 12:26-29 (2000) in IDS) in view of Makarova et al., Gribble et al. (Org. Prep. Proc. Int. v. 17, p. 317-384 (1985)), March (March's Advanced Organic Chemistry, 5th ed. (2001), Wiley, p. 2083), and Makarova-2 (Russian Journal of General Chemistry, Vol. 37, No. 8, 2001, pp. 1099-1101.).

### ***Double Patenting***

Claims 4 and 5 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-2 of copending Application No. 11/989100.

In response, applicant requests that the issue be deferred until the application is otherwise in condition for allowance. Therefore, **this rejection is maintained.**

### ***Other Relevant Prior Art***

The examiner would like to make the following relevant prior art references of record:

Deeter et al. (Tetrahedron Lett., V. 31, No. 49, pp. 7101-04 (1990));

Bartoli et al. (J. Chem. Soc. Perkin Trans. I, 537-543 (1994)).

### ***Conclusion***

The claims are not in condition for allowance. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT HAVLIN whose telephone number is (571)272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Joe McKane can be reached at (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert Havlin/  
Examiner, Art Unit 1626

/Rebecca L Anderson/  
Primary Examiner, Art Unit 1626